Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Post-Ugi Cascade Transformations for Accessing Diverse Chromenopyrrole Collections

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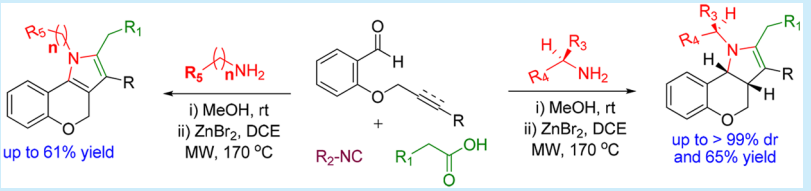
Supporting Information



ABSTRACT: Employing a build/couple/pair strategy, a serendipitous one-pot protocol for the diastereoselective construction of diverse collections of chromenopyrroles is described. This methodology features an unprecedented five-step cascade including azomethine ylide generation followed by in situ intramolecular [3 + 2]-cycloaddition. Furthermore, this protocol was extended to access enantiopure chromenopyrroles using amino acids as chiral auxiliary. Moreover, postpairing reactions were employed to increase the diversity and complexity of our pilot compound collections.

The burgeoning interest in phenotypic screening as an alternative tool to target-based screening[1a,b] has been validated by a recent FDA study finding that more first-in-class small molecules were discovered using the former method.[2a] In this context, a great challenge in a phenotypic-screening campaign is the development of modular synthetic procedures for the rapid access of complex compound collections possessing the stereochemical and skeletal diversity needed for comprehensive structure−activity relationship (SAR) studies. Privileged substructure diversity-oriented synthesis (pDOS) is a prominent tool for generating and identifying small molecules that can modulate disease-relevant protein functions.[2,3] Among the attractive structural options are the chromenopyrrole analogues exemplified by the marine alkaloids ningalin B (**A**) and lamellarin D (**B**), which display a variety of biological activities including potential treatments for CNS disorders (Figure 1).[4−6] Additionally, chromenopyrrole derivatives were also reported to possess anticancer, antimicrobial, antioxidant, and antileishmanial activities.[7−9]

Owing to their remarkable biological activities, many synthetic methods have been developed to access chromenopyrrole derivatives (see the Supporting Information).[8,10] Strategies to access these scaffolds include 1,3-dipolar cycloaddition via base-catalyzed deprotonation of amino acids;[10k] azomethine ylide cycloaddition;[4g] a three-component synthesis combining a 4-aminocoumarin, aldehydes, and nitromethane;[10m] and a Pd(II)-catalyzed oxidative annulation of 4-aminocoumarins with alkynes.[10n]

Although these protocols are useful methods for the synthesis of chromeno[4,3-*b*]pyrroles, they require multistep reactions, long reaction times, and expensive catalysts and reagents and allow low structural variability of the reactants. During our ongoing studies of efficient one-pot methodologies to prepare privileged substructures present in biologically significant compounds,[11] we encountered an unprecedented cascade reaction that provides a conceptually distinct approach to the synthesis of functionalized chromenopyrroles; it is reported here.

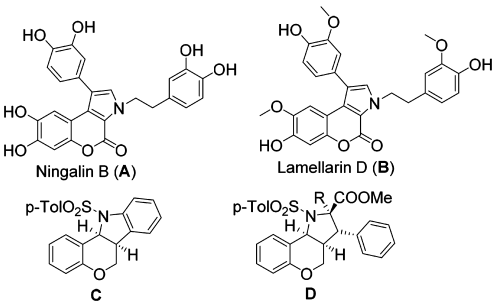


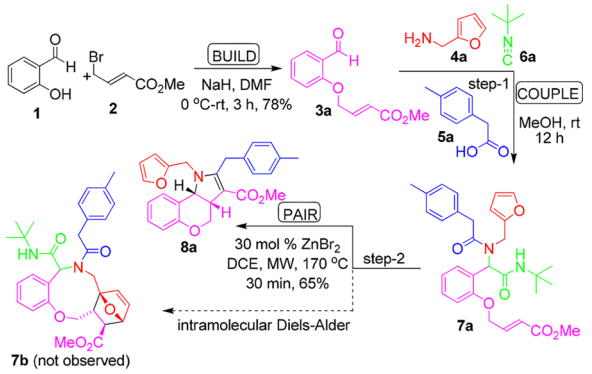
Figure 1. Representative bioactive chromenopyrrole structures.

The serendipitous cascade reaction was discovered while attempting the synthesis of the 9-membered ring system, benzo[*b*,*g*][1,5]oxazonine **7b** (Scheme 1).[10o] The initial synthetic design was inspired by our previous utilization of compound **3a** to access complex oxazepine scaffolds.[11c] To test our intramolecular Diels−Alder reaction scheme, the model substrate **7a** was prepared using a four component Ugi protocol.

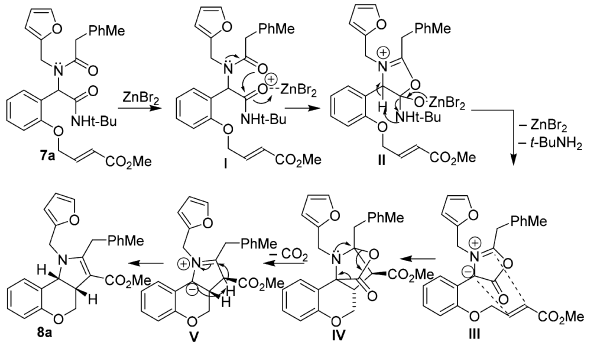
Received: December 22, 2017

DOI: 10.1021/acs.orglett.7b03986
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Zinc Bromide Unexpected Cascade Leading to the Formation of Tricyclic Chromeno[4,3-*b*]pyrrole 8a



Scheme 2. Proposed Mechanism for the Formation of Chromenopyrrole Systems



Unfortunately, subjecting **7a** to a broad set of catalysts and reaction conditions failed to induce formation of Diels–Alder product **7b**, leading only to recovery of **7a** or formation of complex reaction products. Nevertheless, we were delighted to find that using $ZnBr_2$ catalysis gave a single, yet unexpected, product. Extensive spectroscopic analysis unambiguously identified this compound as chromeno[4,3-*b*]pyrrole **8a**, isolated in 65% yield. This sequence has turned out to be a general approach to these structures, and here we report its successful employment with functionalized carboxylic acids, amines, isocyanides, and Michael acceptors to generate a set of diversely substituted chromenopyrroles (see Scheme 3).[12]

As described in Scheme 1, our synthetic plan contemplated systems of type **8a**, which were to be constructed by utilizing a build/couple/pair strategy.[13] In this, the build stage begins with the synthesis of compound **3a** obtained by reacting 2-hydroxybenzaldeyde (**1**), with *trans*-4-bromobutenoate (**2**) employing a traditional S_N2 reaction (Scheme 1). The couple stage then involves the use of an Ugi-multicomponent reaction (MCR), which combines the key building block **3a** with commercially available components (e.g., **4a**, **5a**, and **6a**) leading to dipeptides of type **7a**. The reactive functionalities present in compound **7a** were then paired through a tandem acylation/azomethine ylide formation/cycloaddition process. To optimize the conditions for this serendipitous cascade, many Lewis and Bronsted acids were screened as possible promoters of the desired reaction, including, $Sc(OTf)_3$, TFA, and AcOH. With the first two, in a variety of solvents and at a range of temperatures under anhydrous conditions, no significant clean reaction occurred. When catalytic or equimolar quantities of acetic acid were used, substantial decomposition was observed. Ultimately, it was discovered that $ZnBr_2$ in dichloroethane (DCE) under MW conditions provided the ideal conditions to promote the desired cascade. Thus, we were delighted to observe the efficient and diastereoselective formation of tricyclic chromenopyrrole **8a** in 65% yield by using 30 mol % of $ZnBr_2$ under microwave irradiation at 170 °C.

We then turned our attention to propose a plausible mechanistic pathway of this cascade (Scheme 2). First, coordination of the metal salt $ZnBr_2$, in **I**, catalyzes the *O*-acylation by the tertiary amide leading to the tetrahedral intermediate **II**. Rearrangement of the latter followed by abstraction of the benzylic proton by the expelled strong base *t*-BuNH group led to the generation of azomethine ylide **III**. Consequently, intramolecular [3 + 2]-cyclization (as we have assumed, Scheme 2) should deliver the highly strained intermediate **IV**. Expulsion of the carbon dioxide from the oxazolidinone **IV** should deliver the second azomethine ylide **V**. Subsequent 1,4-proton migration proceeds to give the chromenopyrrole final product **8a** with the most stable cis ring fusion. The fact that no reaction occurs in the absence of the $ZnBr_2$ catalyst provides corroboration for the hypothesis that the initial step involves *O*-acylation reaction leading to the oxazolidinone intermediate **III** through the proposed azomethine yilde intermediate. Many additional experiments in which the same coupling was attempted in the absence of $ZnBr_2$ led only to the recovery of the Ugi product, with no evidence of the cyclized product **8a**.

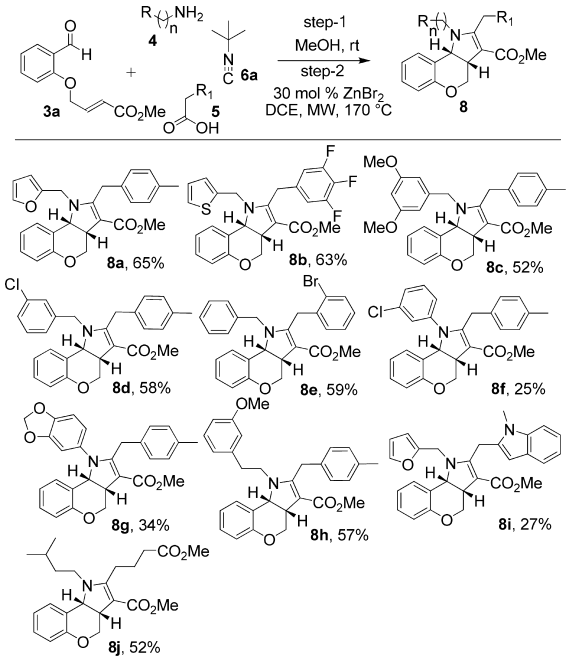
The stereochemistry around **8a** was elucidated using 1D- and 2D-NMR spectroscopy. The chemical shift of the pyrrolidyl methine proton (H_a) in **8a** appeared at δ 4.50 ppm as a doublet (J = 8.0 Hz), consistent with *cis* ring fusion. The two protons at the pyrrolidylbenzopyran ring fusion also showed strong reciprocal NOESY interactions, unambiguously confirming a *cis* relationship (Figure 1, SI). To understand the stereochemistry obtained for **8a**, one needs to consider its two most accessible conformations **A** and **B** (Figure 2, SI). The structural elements in conformer **C** (59 kcal/mol) are such that steric bias is minimal and more conducive, favoring the formation of the *cis* product after 1,4-proton rearrangement. The situation is precisely reversed in intermediate **D** (177 kcal/mol), where the potential for substantive steric compression is obvious. Therefore, intermediate **C** should be thermodynamically more relevant intermediate furnishing the *cis* product.

With successful reaction conditions defined, the generality of the method was evaluated by preparation of a broad set of analogues of **8a**, shown in Scheme 3. All of the amine and acids tested led to the expected products. Altering the aromatic substitutions on the methylamine and the phenylacetic acid was readily accommodated (**8b–e**). Changing the benzylamine component to an aniline derivative also gave the product, with a changed skeleton, but in reduced yield, perhaps because of the reduced nucleophilicity of the amine (**8f**, **8g**). Alternatively, increased steric congestion around the azomethine ylide with the *N*-phenyl substitution could be lowering the yields for **8f** and **8g** (Scheme 2). Changing the nitrogen substitution to 2-phenethyl (**8h**) or isopentyl (**8j**) also led to good yields. The latter two cases also carried *n*-alkyl substitution in place of the aryl acetic acid component. Changing the starting phenyl acetic acid to 2-indole (**8i**) led to the expected product albeit in modest yield.

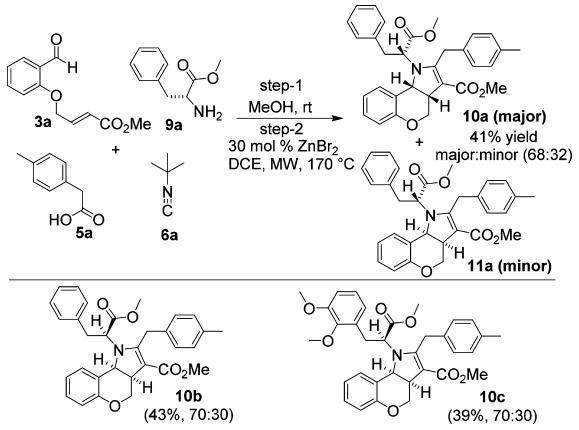
As a further step in building stereodefined products, the amino acid phenylalanine was included in this study (Scheme 4). This would have the advantage of potentially controlling absolute stereochemistry. Both D- and L-phenylalanine (**9a** and **9b**) were

DOI: 10.1021/acs.orglett.7b03986
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Preparation of Various Polysubstituted Chromenopyrroles



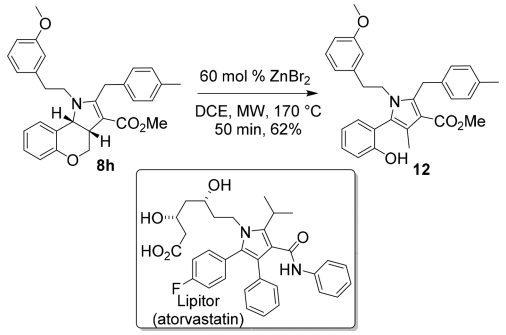
Scheme 4. One-Pot Synthesis of Enantiomerically Pure Chromenopyrroles



used as the amine, as well as L-3,4-dimethoxyphenylalanine (**9c**), in the initial Ugi coupling step. The additional steric hindrance on the amine was well tolerated in the reaction sequence, yielding the product in 39−43% yield. The three amines all gave a mixture of two diastereomers (**10a−c** and **11a−c**). In each case, the mixture of **10** and **11** was formed in a ratio of ca. 7:3. The relative stereochemistry between the phenylalanine starting reagent, which remains untouched in the reaction sequence, and the stereochemistry of the pyrrolidine−pyran ring fusion was proved using NMR spectroscopic analysis relationship (see Figure 3, SI).

An additional step can be added to this reaction cascade, adding tetrasubstituted pyrrole products to the set of compounds that can be prepared with this chemistry. The reaction is shown in Scheme 5 with **8h** as the substrate. Polycyclic dihydropyrrole **8h** was subjected to similar conditions used to prepare it, but doubling the amount of $ZnBr_2$. Under these conditions, the phenol ether underwent elimination, and isomerization gave the pyrrole in 62% yield (for a proposed mechanism, see Scheme 2, SI). The potential for preparing medically important products

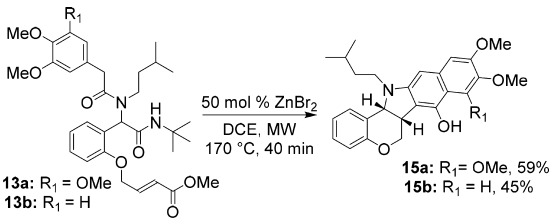
Scheme 5. Post-Pairing Reaction Leading to Tetrasubstituted Chromenopyrroles



using this chemistry is apparent when comparing the structure of **12** with the important cholesterol-lowering drug Lipitor.

A second postpairing application, the synthesis of the novel compounds, tetrahydrobenzo[*f*]chromeno[4,3-*b*]indol-7-ol derivatives, is shown in Scheme 6 using 3,4,5-trimethoxy- and 4,5-

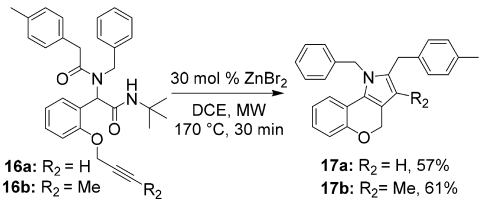
Scheme 6. Post-Pairing Reaction Leading to Tetrahydrobenzo[*f*]chromeno[4,3-*b*]indol-7-ol Systems



dimethoxyphenylacetic acids as the acid component in the Ugi coupling step. Subjecting substrates **13a** and **13b** to 50 mol % of $ZnBr_2$ at 170 °C under microwave irradiation for 40 min gave directly **15a** and **15b** in 59% and 45% yield, respectively. Cyclization to give an additional ring by Friedel−Crafts acylation was not a significant pathway even with electron-rich products such as indole **8i**; however, with the additional Lewis acid the pentacyclic products **15** could be produced, presumably through intramolecular Friedel−Crafts acylation of the di- and trimethoxybenenes (for a proposed mechanism, see Scheme 3, SI).

A third version of this reaction cascade provided a more direct synthesis of pyrroles. Substituting a propargyl unit for the 4-substituted butenoate, propynyl and butynyl substrates **16a** and **16b** were prepared. While the alkynes lack the activating electron-withdrawing ester, they nevertheless underwent cycloaddition with the postulated azomethine ylid intermediate to give **17a** and **17b**, respectively, in very reasonable yields (Scheme 7). These successful reactions are indicative of the broad applicability of this preparative chemistry.

Scheme 7. Synthesis of Tetrasubstituted Chromenopyrroles



DOI: 10.1021/acs.orglett.7b03986
Org. Lett. XXXX, XXX, XXX−XXX

To gain insight into the drug-likeness of the synthesized compounds, we have calculated the relevant molecular descriptors for prediction of standard physicochemical parameters linked to the oral bioavailability and drug-likeness pattern according to the Lipinski "rule of five".[14] Most of the compounds are compliant with the Lipinski rules attributed to the nature of lead drug candidates (for discussion and calculated parameters, see the SI).

In summary, the novel one-pot cascade methodology described above is a broadly reliable and versatile tool for the synthesis of a range of polysubstituted chromenopyrrole scaffolds. The substrate scope is large and the diastereoselectivity and the isolated yields are high under a single set of reaction conditions, suggesting that diverse targeted libraries should be readily synthesized using this protocol. Gratifyingly, in situ intramolecular generation of a transient azomethine ylides avoids the need for the more exotic approaches described in the literature. Furthermore, the methodology provided access to enantiomerically pure products when amino acids were used as the reaction partners, hence increasing the 3D-diversity of our pilot compound collection. In addition, the use of postpairing transformations increased the complexity of our small library.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03986.

Previous approaches, stereochemical analysis, druglike properties, mechanisms, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by generous grants from Al Jalila Foundation, UAE (Grant No. AJF201531) and the Research Funding Department, University of Sharjah-UAE (Grants Nos. 15011101007 and 15011101002).

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DOI: 10.1021/acs.orglett.7b03986
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